PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference A31696M	**FOR FURTHER ACTION**	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
International application No. PCT/JP 03/15968	International filing date *(day/month/year)* 12.12.2003	Priority date *(day/month/year)* 16.12.2002
International Patent Classification (IPC) or both national classification and IPC C07D401/14		
Applicant MITSUBISHI PHARMA CORPORATION		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 5 sheets, including this cover sheet.

   ☐ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the opinion
   - II ☐ Priority
   - III ☐ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☒ Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
   - VI ☐ Certain documents cited
   - VII ☐ Certain defects in the international application
   - VIII ☐ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
19.02.2004	07.03.2005
Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized Officer Von Daacke, A Telephone No. +49 89 2399-8286

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/JP 03/15968

I. Basis of the report

1. With regard to the **elements** of the international application *(Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17))*:

Description, Pages

1-46 as originally filed

Claims, Numbers

1-10 as originally filed

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

   These elements were available or furnished to this Authority in the following language: , which is:

   ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).

   ☐ the language of publication of the international application (under Rule 48.3(b)).

   ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

   ☐ contained in the international application in written form.

   ☐ filed together with the international application in computer readable form.

   ☐ furnished subsequently to this Authority in written form.

   ☐ furnished subsequently to this Authority in computer readable form.

   ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

   ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

   ☐ the description, pages:

   ☐ the claims, Nos.:

   ☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)).

   (Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-10
	No:	Claims	
Inventive step (IS)	Yes:	Claims	
	No:	Claims	1-10
Industrial applicability (IA)	Yes:	Claims	1-10
	No:	Claims	

2. Citations and explanations

see separate sheet

V REASONED STATEMENT

1. PRIOR ART

The documents cited in the International Search Report
D1: WO00/18758
D2: WO01/70728
D3: WO01/70729
have been considered for the examination procedure.

2. NOVELTY

The claimed subject-matter is considered to be novel (Article 33(2) PCT). The essential structural difference between the claimed compounds and those of D1 relates in the presence of the dihydropyridine substituent in position 2.

3. INVENTIVE STEP

The claimed subject-matter does not fulfil the requirements of Article 33(3) PCT for the following reasons.

The closest state of the art for the present application is represented by D1. D1 discloses structurally similar compounds which may be used in the treatment of diseases caused by abnormal activity of TPK1. In the present application, the structural variation of the D1 compounds, namely the choice of a specific 2-substituent and the alkylation at the pyrimidine nitrogen atom (position 3) is alleged to lead to derivatives with the same qualitative activity as those described in D1. In view of the experimental part and the other information as given in the description, it can be assumed that this problem has been solved for the compounds according to Claim1.
The problem underlying the present application can, however, not be seen in the provision of further novel pyrimidin-4-one derivatives, because the proposed solution would be seen as obvious.
D1 teaches that R^1 (position 2) may be a heterocyclic substituent. In the description

on page 13, a list of various different moieties is disclosed, including different aromatic, partially saturated and saturated heterocyclic systems. Inter alia, pyridine and piperidine are mentioned, but not dihydropyridine. D2 discloses similar compounds. The 2-substituent may be dihydropyridine which is condensed. A man skilled in the art, aware of the disclosure of D1 and D2, would have obviously expected the same qualitative properties shown by the compounds of D1 and D2 also for the present compounds wherein the 2-substituent represents a dihydropyridine group. The alkylation of the nitrogen (R^1) is finally known from the structurally very close D3 compounds.

Therefore, the problem underlying the present application should be seen in the provision of new pyrimidone derivatives having unexpected properties over those of the closest prior art compounds (D1). In the absence of comparative test results or other appropriate information it is not possible to decide whether such a problem has been solved or not. In the case where comparative tests are envisaged in order to support an inventive step, these must be carried out between the compounds of the present application having the maximum structural similarity with the compounds of the closest prior art, such that the effect is shown to have its origins in the distinguishing feature of the claimed invention.

4. INDUSTRIAL APPLICABILITY

No objection.